# Outcome of the First Trimester Threatened Miscarriage: Study of the Predicting Factors

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**ABSTRACT:**

**BACKGROUND:**

Threatened miscarriage is a distressing condition to both pregnant woman and gynecologist. It is important to predict the outcome of threatened miscarriage through maternal history, biochemical tests, and fetal ultrasound for patient counseling and to avoid delay in management.

*Study design*

A prospective multiple logistic regression analysis study.

**OBJECTIVE:**

To assess the power of factors which are maternal history (age, vaginal bleeding, parity and hypertension), biochemical tests (β-hCG & serum progesterone level) and fetal ultrasound (crown rump length& fetal heart rate) for predicting the outcome of pregnancy (fetal demise & ongoing pregnancy) complicated by threatened miscarriage between 7-11 wks and to determine the time interval from onset of symptoms to fetal demise development.

**PATIENTS AND METHODS:**

The study was carried out on 80 pregnant women at their 7-11 weeks of gestation suffering from vaginal bleeding attending Al-Elwiya Maternity Teaching hospital. They were subjected to ultrasound to confirm fetal viability, assay of serum progesterone and β-hCG levels and pain with bleeding scores. All these were repeated on weekly basis for four weeks follow up to monitor the pregnancy and identify the period to fetal demise (if happened). The data is gathered on questionnaire paper and then subjected to statistical study.

**RESULTS:**

The β-hCG (human chorionic gonadotrophin hormone) level was found to be the main predictor for pregnancy outcome (miscarriage/fetal demise & ongoing pregnancy) and highly statistically significant (P value<0.0012), followed by bleeding (p <0.002) and maternal age (p<0.01) respectively, while other variables (serum progesterone, fetal ultrasound, parity) showed no statistically significant effect (P value=0.47, 0.63, 1.146 respectively) on the risk of miscarriage/fetal demise. Serum progesterone level was highly significant in predicting ongoing pregnancy (P value=0.001)

**CONCLUSION:**

Measuring of beta hCG levels is found to be a good predictor for the outcome of the first trimester threatened miscarriage whether ends in to fetal demise or continuing pregnancy, while other factors like ultrasound, serum progesterone levels and parity are useful in assessing an ongoing pregnancy but have no power in predicting possibility of fetal demise. Also measuring the interval from the onset of bleeding to fetal demise development can be useful to avoid delaying pregnancy management.

**KEY WORDS**: first trimester, threatened miscarriage, predicting factors

## INTRODUCTION:

Fetal loss is a common pregnancy complication occurring in about 15% of clinically recognized pregnancies. Threatened miscarriage is a pregnancy complicated by vaginal bleeding and/or uterine cramps before 20 weeks of gestation [1,2]. The bleeding is usually resolves spontaneously in few days and may never to recur, or it may continue, or stop and start over several days or weeks .When abdominal cramps supervene that the process may become inevitable especially when cervix opens [3]. Spontaneous miscarriage occurs in around 10%-

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20% of confirmed pregnancies and is associated with psychological and physical morbidity [4].

This risk is highest in early pregnancy. Evidence from studies of hCG [human choionic gonadotropins] assays in very early pregnancy suggests that rates of such early miscarriage may be high as 50%-60% [5]. Over 80% of miscarriage occurs in the first 12 weeks of pregnancy [6].

Karyotypic abnormalities have been observed in about 50% of spontaneous abortions. (numerical chromosome abnormalities such as autosomal trisomies , monosomy X , triploidy and tetraploidy) [1], while CMV, rubella, toxoplasmosis, listeria, ureaplasma, and syphilis all are uncommon cause of early abortion [6]. Fever of 37.7C or more is well recognized risk of miscarriage [7]. Polycystic ovary syndrome women have increased risk of both sporadic and recurrent miscarriage attributed to high circulating levels of luteinizing hormones in the luteal phase [5].

 UP to 30% of pregnancies in patients with poorly controlled diabetes mellitus result in spontaneous miscarriage The risk appears related to the degree of metabolic control in early pregnancy. Thyroid hormone deficiency effect on early pregnancy loss have not been adequately studied. Thyroid auto antibodies alone have been associated with an increased incidence of miscarriage. Abnormalities of reproductive tract including Congenital or acquired defects i.e uterine synechiae [6], Fibroids, Cervical incompetence. Immunological factors, Trauma, either direct to the uterus or indirect as surgical removal of ovary containing corpus luteum of pregnancy [8]. Unexplained,  at least 50% of sporadic miscarriage has no identifiable cause [5].Maternal obesity, increase maternal age, previous miscarriage and higher gravidity are risk factors for increasing chance of miscarriage[9,10].

## AIMS OF THE STUDY :

Are to assess the value of maternal history, biochemical tests (free beta hCG  and serum progesterone) and fetal U/S measurements for predicting pregnancy outcome in first trimester threatened miscarriage and determining the time interval to fetal demise development.

## PATIENTS AND METHODS:

This prospective multiple logistic regression analysis carried out in  the Department  of Obstetrics  &  Gynecology  at    AL-Elwiya Maternity  Teaching Hospital , Baghdad, Iraq, from 1st May 2012 to end of July 2013. The study protocol includes a questionnaire for

addressing the population of interest information (name, age, occupation, address, LMP, medical disease, smoking, serum B-hCG, progesterone level, fetal U/S) and the exposure and outcome considered. The study was approved by the Arab Board committee and the hospital scientific league.

Out of 118 pregnant women recruited for the study while attending the outpatient and antenatal clinics of the hospital. A verbal consent was obtained and the idea of the study was explained to them. Only 80 pregnant with a single viable pregnancy suffering from threatened miscarriage were included and the remaining were twin, molar and ectopic pregnancy and those in whom pregnancy was ended by inevitable or complete abortion had all been excluded.

The work up includes studying of maternal characteristics (pain and bleeding severity ) and a weekly assessment of serum progesterone, hCG and fetal ultrasound  measurements for four weeks period between 7-11 weeks of gestation.

A detailed history and thorough examination were performed and the gestational age  was determined depending on accurate dating of last menstrual period and confirmed by ultrasound , which confirms viability and excludes other pathology. Phone number of participants registered on the questionnaire for follows up.

Maternal age, parity, gestational age, serum B-hCG and serum progesterone level, fetal ultrasound measurements, amount of bleeding, presence of maternal disease were included in the questionnaire for statistical matching and analysis.

The participants were informed to attend the hospital for weekly assessment to record any presence of pain and bleeding, to measure serum progesterone, hCG level, and to do fetal ultrasound measurements for four weeks duration (length of the study).

The goal of the 4 weeks follow up is to ensure adequate time to monitor pregnancy ( ongoing or fetal demise) and to detect signs of fetal demise that complicating the threatened miscarriage  and to determine the period of time from first attendance to the development  of fetal demise.

In each visit, a 5 ml of blood was collected from the participants and serum separated and centrifuged. The serum then stored at 2-8 c for 24 hours and for longer periods, the sample stored at -70 c .Serum hCG, progesterone was measured

by radio-immuno assay(RIA) method . Ultrasonographic examination was performed by the specialist at outpatient department of the hospital. The diagnosis of miscarriage was confirmed by the presence of a fetal pole more than 10 mm with no fetal heart or, the gestational sac was more than 25mm with no fetal pole.

*Statistical analysis:* SPSS (statistical package for social sciences) was used for entering the data and statistical analysis. Descriptive statistics were presented as mean ± SD (standard deviation) for age, HCG level and time interval. Other variables were presented as frequencies and proportions (%). Multiple logistic regressions was used to assess the effect of study variables as predictors for the risk of miscarriage as an outcome, the odds ratio of the risk of each predictor was calculated with a (95%) confidence interval. The positive correlation coefficient [beta value (*B*)] indicates a positive effect of the predictor on the measured outcome, while the negative signed (*B*) indicates an inverse effect on the risk of having the measured outcome (miscarriage). The higher odds ratio, given that significant, indicates higher risk predictor variable. Level of significance (P.

value) of $\leq 0.05$ considered as significant prediction.

## RESULTS:

A total of (118) pregnant women were recruited for this study at their 7th weeks of gestation, a singleton intrauterine pregnancy with a live fetus was found in (95) cases, twin pregnancy seen in (3) cases, missed abortion in (5), ectopic pregnancy in ( 3), molar pregnancy in (1) case and in (11) cases an empty gestational sac was discovered and in the second scan one week later, a live fetus found in only (7) patients, so we had (102) patients with single viable pregnancy and all cases with twin, molar and ectopic were excluded. Moreover during the follow up period (10) women dropped out of the study and (12) cases of inevitable, incomplete and complete abortions were also excluded so, the remaining number of participants was (80) pregnant with a single viable pregnancy suffering from threatened miscarriage.

Figure 1: Shows percentage of women with threatened miscarriage in whom healthy pregnancy outcome was 78.75% (63) and 21.25% (17) developed miscarriage ( fetal demise).
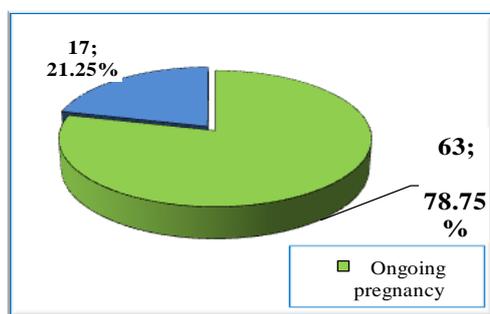


**Figure 1: Outcome distribution among study group (N=80)**

Table (1) shows the general characteristics of the participants. The mean age was (26.7 ± 6.3) years, most of them were urban (71%) & 80% were multipara and small number of them were hypertensive.

**Table 1: General characteristics of study women (N=80).**

| Variable | | Number | % |
|---|---|---|---|
| Age (years) | 16 - 25 | 35 | 43.75 |
| | 26 - 39 | 45 | 56.25 |
| | Mean ± SD* | 26.7± 6.3 | - |
| Residence | Urban | 57 | 71.25 |
| | Rural | 23 | 28.75 |
| Parity | Primi | 10 | 12.5 |
| | < 5 | 64 | 80.0 |
| | ≥ 5 | 6 | 7.5 |
| Antenatal Booking | Yes | 50 | 62.5 |
| | No | 30 | 37.5 |
| History of hypertension with pregnancy | Positive | 25 | 31.25 |
| | Negative | 55 | 68.75 |

\* SD; standard deviation

while 5 cases within 14days and the last 3 women within 21 days. The mean time interval for the 17 miscarried women was (11.52 ±5.33) days.

Figure (2) describes the time interval between onset of bleeding and miscarriage ( fetal demise), was 7 days in nearly most of them (9 cases),
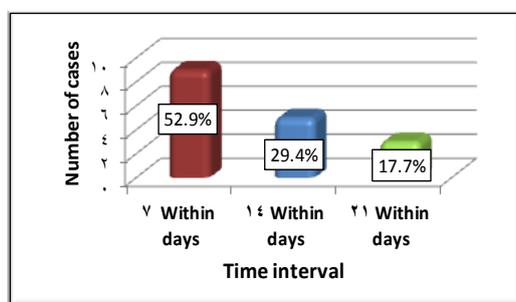


Figure (2) time interval between onset of bleeding and miscarriage

Table (2) reveals that miscarriage directly correlated with the maternal age; number of miscarriages had been increased significantly with the advancing age, P=0.03.

**Table 2: Distribution of maternal age in 17 miscarried women.**

| Maternal age (years) | No. | % | P |
|---|---|---|---|
| 16 - 20 | 2 | 11.76 | |
| 21 - 25 | 1 | 5.88 | |
| 26 - 30 | 2 | 11.76 | 0.03 |
| 31 - 35 | 4 | 23.53 | |
| 36 - 39 | 7 | 41.18 | |
| Total | 17 | 100.0 | |

***Distribution of gestational age in miscarried women***

It had been observed that 10 (58.82%) of the 17 miscarriages had occurred at gestational age of 7 - 9 weeks, and 7 miscarriages (41.18%) had occurred at gestational age of 9 - 11 weeks.

Distribution of hCG and serum progesterone in study women shown in table (4), the mean B-hCG level of women with ongoing pregnancies was significantly higher than those with miscarriage, (12,473.00± 5,256.00 vs. 4,152.00 ± 2,123.00) mIU/ml, respectively, P<0.001.

On the other hand serum progesterone was significantly higher in women with ongoing pregnancy than those with miscarriage (24.82 ± 5.82 vs. 13.18 ± 6.21) ng/ml respectively, P<0.001.

**Table 4: The mean hCG and S. progesterone levels in studied women with pregnancy outcome.**

| Parameter | Ongoing pregnancy  (n=63) | Miscarriage (n=17) | P |
|---|---|---|---|
| B-hCG mIU/ml | 12,473.00± 5,256.00 | 4,152.00 ± 2,123.00 | <0.001 |
| S. progesterone ng/ml | 24.82 ± 5.82 | 13.18 ± 6.21 | <0.001 |

Distribution of hCG levels and gestational age shown in Figure (3) it had been significantly found that hCG level of women with ongoing pregnancy had a rising up trend, it increased from 3324 mIU/ml at the 7th week of gestation to reach 32370 mIU/ml at the 11th week, P=0.00012. In contrast, in those women who miscarried, hCG level tend to decreased with the advancing gestational age it was 2086 mIU/ml at the at the 7th week of gestation and reached 224 mIU/ml at the 11th week, P<0.0002.
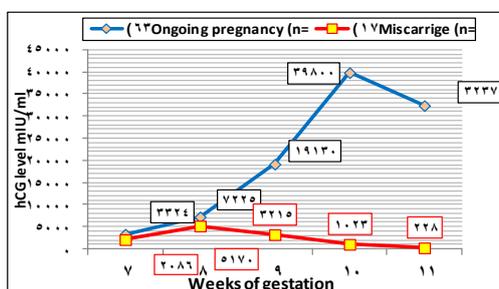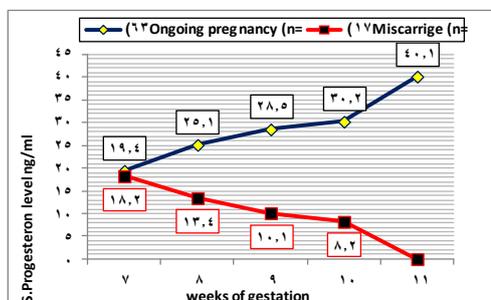


**Figure 3: Changes in mean hCG level with advancing gestational age.(P=0.00012 in ongoing pregnancy group, P= 0.0002 in miscarriage group.)**

The same significant trends of hCG, had been noticed in S. progesterone; the serum progesterone level had been significantly increased with gestational age in women with ongoing pregnancies, while significantly decreased in women with miscarriage, in both comparison P=0.05.



**Figure 4: Changes in mean S. progesterone level with advancing gestational age. (P=0.0031 in ongoing pregnancy group, P= 0.0011 in miscarriage group)**

Table (5) describes the distribution and comparison of severity of pain with bleeding among miscarried women vs. those with ongoing pregnancy, revealed significantly, that miscarried women were about 5 folds (odds ration; 4.81) more likely to have severe pain and bleeding than those with ongoing pregnancies, while mild pain and bleeding more are frequent among women with ongoing pregnancies, P=0.0018.

**Table 5: Comparison in severity of pain and bleeding between ongoing pregnancy and miscarried women groups.**

| Severity of pain with bleeding | Ongoing Pregnancy | | Miscarriage | | Total | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Sever pain and bleeding | 13 | 16.3 | 25 | 31.3 | 38 | 47.5 |
| Mild pain and bleeding | 30 | 37.5 | 12 | 15.0 | 42 | 52.5 |
| Total | 43 | 53.8 | 37 | 46.3 | 80 | 100.0 |
| Odds ratio = 4.81  95%CI (1.86 - 12.4)<br>P.value = 0.0018 | | | | | | |

***Multiple logistic regression analysis of predictors versus pregnancy outcome***
The Multiple logistic regression analysis, using a model included the following variables as predictors; maternal age, hCG level, progesterone level, fetal CRL on ultrasound, bleeding, parity, and hypertension with pregnancy\s, the measured outcome in this model is the miscarriage. It had been significantly found that 3 of these variables are influencing the outcome of pregnancy ( miscarriage/ fetal demise ), which are maternal age (OR =2.43; p<0.01) which is positively influencing the outcome, as the maternal age increases the risk of miscarriage be higher, hCG level shows inverse effect on the measured outcome , the lower level of HCG has the higher risk, (OR=3.2; P=0.0012), bleeding shows a positively significant correlation with miscarriage, (2.81; P=0.002), the more bleeding, the higher the risk of miscarriage. The other predictors in the models show no significant correlation with miscarriage. Hence, free B- hCG level was the main predictor for the pregnancy outcome followed by bleeding and maternal age, respectively.

Table 6: Multiple logistic regression analysis for predictors of miscarriage in 17 miscarried women.

| Predictor | correlation coefficient (B) | Significance (P.value) | OR (95%CI) |
|---|---|---|---|
| Constant | 1.651 | <0.001 | - |
| Maternal age | 1.37 | 0.004 | 2.43 (1.33-4.87) |
| B-hCG level | -2.561 | 0.0012 | 3.2(3.11-5.78) |
| Serum progesterone | 0.108 | 0.47 | 1.14 (0.85-1.38) |
| Fetal CRL | -0.003 | 0.63 | 1.27(0.73 - 2.21) |
| Bleeding | 1.54 | 0.002 | 2.81 (2.1 - 4.8) |
| Parity | 1.146 | 0.29 | 1.12 (0.38-2.04) |
| Hypertension with pregnancy | 1.094 | 0.38 | 1.62 (0.25-5.13) |

## DISCUSSION:

This study showed an increase risk to fetal demise with increasing maternal age, 41.18% of them had miscarriage at age 36-39 years which is highly significant (p=0.03), and agrees with **Blohm et al.** who reported in 2008 a prospective longitudinal population – based study of clinical miscarriage according to maternal age in Swedish women was as follows : 20-24 years 13.5%, 25 , 25-29 years 12.3%, 30-34 years 10.3%, 35-39 years 17.5%. Clinical miscarriage constituted 12% of all pregnancies and one in four women who had been pregnant up to 39 years had experienced a miscarriage which not influenced by the order of pregnancy, smoking, regular exercise [11]. Our results also agree with **Anne et al** findings who estimated the association between maternal age and fetal demise, the risk of spontaneous abortion was 8.9% in women aged 20-24 years & 74.7% in those aged 45 years or more [12]. In addition, **Maconochie et al.** examined in a case control study on 600 women aged 18-55 years old the effect of life style risk factors (smoking, drinking, diet) on miscarriage founded after adjustment for these confounders increase maternal age as independent risk factor for increase risk of miscarriage[13].

The severity of pain with bleeding showed a fivefold increase in risk of miscarriage, and a significantly high increase of miscarriage in patients with severe pain & bleeding (OR=2.81, P=0.002) when comparing the severity of pain with bleeding among miscarried women versus those ongoing pregnancy, these results agree with **Hasan et al.** they enrolled 4510 women to estimate whether first trimester vaginal bleeding was predictive of subsequent miscarriage, they founded that heavy bleeding particularly with pain was high risk for miscarriage (OR=3), with three times the risk of women without or light bleeding (OR=1.1). our study founded that the time interval between onset of bleeding and miscarriage and most of miscarriages occurred within 7 days and mean time interval was ( 11.52 ±5.33) days [14].

However, **Gracia et al** evaluated the association the risk of severe pain and bleeding with the first trimester miscarriage in case control study on 467 women (between 25-35 years), the complaint of bleeding (OR=7.35) were strongly associated with miscarriage and the pain was negatively associated with miscarriage (OR=0.72) which does not go with our figures for pain severity (OR+2.81, P. value= 0.002) reported in this study for predicting pregnancy outcome [15].

Fetal U/S measurements (CRL, FHR) were found insignificant (OR=1.27, P=0.63) in detection of fetal demise, a similar finding reported by **Makrydimas et al**. in 2003 who did a prospective regression analysis study on 2139 women in Greece, and examined the association between the demographic characteristics (maternal age, gestation, history of vaginal bleeding) with transvaginal ultrasound parameters (fetal heart rate, CRL, gestational sac diameter) and outcome

of first trimester pregnancy. They found the relationship of small gestational sac and fetal bradycardia to subsequent fetal loss in pregnancies with a life fetus at 6-10 weeks of gestation, but in same time they proved no significant difference in ultrasound parameters between those in which fetal loss occurred within 2 weeks of scan compared to cases in which loss after long interval [16]. In contrast with the study performed by *Celen et al.* in 2012 on 1295 records of patients presented to the Research Hospital Ante natal Clinic in Ankara, Turkey. They assessed the diagnostic utility of the first examination before 11 weeks and found that, it is a valuable tool for predicting pregnancy outcome [17]. *George et al.* in 2011, also demonstrated in a retrospective study that prediction of subsequent miscarriage in singleton pregnancies with a live embryo is provided by maternal history and ultrasound measurements. A logistic regression analysis reported that the increase risk of miscarriage with increase maternal age ( OR=1.05), cigarette smoking (OR=1.91), vaginal bleeding (OR =2.03) and was inversely related to CRL (OR=0.79), heart rate (OR=0,96)[18].

We also reported a positively significant effect of B-hCG on pregnancy outcome (OR=3.2, P=0.0012), while serum progesterone showed no significant effect on detection of fetal demise (OR=1.14, P =0.47), these figures agree with *Maureen et al* who worked on 220 women with first trimester threatened miscarriage, showed that serum progesterone & inhibin-A or serum progesterone & hCG combination improve specificity. Triple biochemistry did not show substantial improvement over dual biochemical strategy, so dual marker strategy might help distinguish viable from non viable pregnancies in early gestation [19].

Similarly *Al-Sebai et al* in 1996 screened in a prospective controlled study on 554 women with first trimester threatened abortion, they showed that single measurement of free B-hCG concentration was 95% C.I (3.75-5069), and the difference between the non-continuing and the threatened ongoing pregnancies was statistically significant (P< 0.00 in all cases).The study suggested possible role for a single serum B-hCG measurement in the immediate diagnosis of early pregnancy failure and in prognosis of viability which agree with our result in that hCG is the main predictor for pregnancy outcome [20].

Serum progesterone was significantly different between both groups (ongoing and miscarried women), significantly increased in ongoing pregnancy (P=0.001) and significantly decreased in miscarried women on multiple logistic regression so that serum progesterone showed no significant correlation with miscarriage (P=0,47) and this might be attributed to the effect of other factors which might overcome the effect of progesterone, in addition to the smaller sample size (only 17 women with miscarriage), further studies on larger sample size might help in evaluation of the effect of progesterone. These results disagree with *Kingsland et al* work on 499 women with threatened miscarriage in the first 18 weeks of pregnant, they showed that single measurement of serum progesterone is valuable in immediate diagnosis of early pregnancy failure and the long term prognosis of viability as serum progesterone level was significantly in non continuing than threatened continuing pregnancies [21].

Additionally our results also disagree with *Hanita et al* in 2012, who made a cross sectional study on 81 Malaysian women under 13 weeks presented with vaginal bleeding (ectopic pregnancy &local causes excluded) using serum progesterone concentration of less than 32.7 ng/ml as cut off value for the diagnosis of non viable pregnancy , the sensitivity was 90%, specificity 92%, and negative predictive value 75% concluded that a single measurement of serum progesterone has a role in determining pregnancy viability [22].

**CONCLUSION:**
This study demonstrated the feasibility of predicting the outcome of pregnancies complicated by threatened miscarriage (ongoing pregnancy or fetal demise). Serum progesterone and fetal U/S cannot be used alone to predict pregnancy outcome as they showed no significance in predicting possibility of fetal demise while they showed a significant correlation with ongoing pregnancy.

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